REMARKS

The interview graciously granted by examiner Vu to applicant's attorney, Anne Kornbau, on March 21, 2007, is acknowledged with appreciation. Per the requirement of the last paragraph of the Interview Summary, applicant provides below the substance of the interview.

The Final Action of December 8, 2006, has been carefully reviewed. The claims in the application remain as claims 1-6, 8, 9, 11-20, 22, 23 and 25-30, these claims being amended as explained below based on the aforementioned interview. Applicant's claims define patentable subject matter warranting their allowance. Applicant respectfully requests favorable consideration, entry of the amendments presented above, and early formal allowance.

During the aforementioned interview, as understood, the examiner agreed that the present invention is patentable over the prior art for the reasons explained during the interview and repeated below. However, the examiner indicated that the functional statement of "an isolating layer" could not be accepted. Accordingly, the independent claims 1 and 29 have been amended to remove the offending language "isolating layer" (and the dependent claims have been conformed), such language being replaced by "hydrophilic polymer layer" which

defines the sub-layer or intermediate layer in a more physical way, support being found for example in claims 9 and 22.

The only other amendments submitted above involve correction of the spelling "nonpareil".

In the final Action, the rejection of claims 1-7, 9, 10, 12-20, 22, 23 and 25-30 as obvious under §103 from Jeary in view of McTeigue and Kamada was repeated, and made final. Applicant respectfully traverses this rejection, and repeats the substance of the aforementioned interview regarding this rejection.

A key point in this regard is the relevant solubility in water of Venlafaxine compared with the solubility of most other anti-anxiety/SSRI compounds which are only slightly soluble in water. These other compounds therefore do not present the same stability problems in formulating an extended release dosage form as exists with respect to the very water-soluble Venlafaxine. Because Venlafaxine is so much more soluble in water than other SSRI's, it needs protection to form a suitable controlled release formulation, and this is what the present invention provides, unlike anything in the prior art or anything which could be gleaned from consideration of the three references together.

The solubility issue is discussed in applicant's specification. At page 1, third paragraph, it is pointed out that Venlafaxine Hydrochloride has a solubility of 572 mg/ml in water, and this is confirmed by attachment A relating to Effexor XR®. The first full paragraph on page 2 of applicant's specification states as follows:

> In some cases, for example with very water soluble active materials and with relatively high doses it is not feasible to produce tablets which enable appropriate control on the drug release. This is the case, for example with Venlafaxine Hydrochloride.

In contrast to Venlafaxine, other anti-anxiety/SSRI's are only slightly soluble in water as evidenced by attachments B through G. Of these, Zoloft® is stated to be only "slightly soluble in water" as is Clomid. Citalopram HBr is said to be "sparingly soluble in water", as is Luvox. Others may be slightly more soluble, but are far less soluble than Venlafaxine.

As pointed out previously, applicant's formulation comprises three distinct layers on top of the core, and these three layers must differ from one another:

1. A layer of Venlafaxine Hydrochloride, which is coated on a nonpareil inert core with water soluble binder.

2. A layer of water-soluble polymer (which may be or may be not the same polymer as the binder). This

isolating/protecting/separating layer (sub-coating) is essential because the Venlafaxine Hydrochloride tends to influence the stability of the outer coating and should be separated by this layer.

3. A layer of hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer (outer coating). This (outer) layer enables the controlled release of venlafaxine hydrochloride.

The sub-layer, i.e. layer 2 above, which is a hydrophilic polymer layer, is very important because the Venlafaxine HCl tends to influence the stability of the outer coating and therefore need to be separated by such sub-coating.

The layer 3 comprising hydrophobic polymer is relatively water-insoluble compared with the sub-layer 2.

As previously pointed out, the main reference (Jeary) focuses on Fluvoxamine which is a poorly water soluble drug. The person of ordinary skill in the art does not learn how to handle a highly water soluble drug like Venlafaxine HCl from the teachings of Jeary because, if Jeary's teachings are adopted for Venlafaxine HCl, a successful result will not be achieved. Control of time release of a poorly water soluble drug like Fluvoxamine, the focus of Jeary, is relatively easy

compared with the problem of how to control a highly water soluble drug like Venlafaxine HCl.

The subsidiary references would not lead the person of ordinary skill in the art to any modification of Jeary which would bring a modified Jeary to the present invention. As pointed out previously, McTeigue exemplifies only the water-insoluble active ingredients. It would not have been obvious for any person skilled in the art that the water-soluble Venlafaxine Hydrochloride would be controllably released from the system disclosed by McTeigue because the solubility of the Venlafaxine chloride strongly affects the rate of release, and as a result, the choice of coating.

Finally, Kamada describes the rotor process and coating seeds in a rotor system, which has nothing to do with any rate controlling of highly soluble materials like the Venlafaxine Hydrochloride. Based on Kamada's teaching, it would not have been obvious for a skilled artesian to prepare formulation suitable for the controlled release of the Venlafaxine Hydrochloride. Furthermore, the choice of coating is not trivial and cannot be learned from Kamada.

The references would not have been obviously combined, as there is no reason or purpose, motive or incentive for the proposed combination. Moreover, even of the combination were obvious (contrary to applicant's positon),

the resultant reconstruction of Jeary in view of McTeigue and Kamada would not reach the claimed subject matter.

Withdrawal of the rejection is in order and is respectfully requested.

As regards commentary in the final action, applicant respectfully points out that while applicant indeed did discuss each of the references individually, as must be done in order to address the content of each reference, applicant also has attacked the proposed combination as not having been an obvious combination, as not leading to the present invention, and furthermore as not reaching the present invention even if obvious (contrary to applicant's position).

A consideration of the references together simply would not have led the person of ordinary skill in the art to solve the problem of the highly water soluble Venlafaxine HCl in an extended release formulation by coating the Venlafaxine HCl on a nonpareil core, providing a hydrophilic polymer layer over the Venlafaxine HCl coating, and then providing a control release polymeric layer comprising hydrophobic materials over the hydrophilic polymer layer.

No rejection was imposed in the final Office Action on the basis of 35 USC 112. Nevertheless, as pointed out above, during the aforementioned interview the examiner

indicated that the language "isolating layer" could not be accepted. This issue is addressed by the amendments submitted above based on support in the previously considered claims 9 and 22.

All issues addressed in the final Action and during the interview are addressed above. Withdrawal of the rejection, entry of the amendments presented above, and formal allowance are in order and are respectfully requested.

Respectfully submitted,

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Effexor XR

Effexor XR®
(venlafaxine hydrochloride)
Extended-Release Capsules

This products label may have been revised after this insert was used in production. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

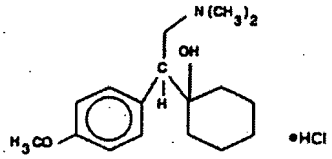
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Effexor XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Effexor XR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Effexor XR is an extended-release capsule for oral administration that contains venlafaxine hydrochloride, a structurally novel antidepressant. It is designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (RMG)-1-[α- [(dimethylamino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride and has the empirical formula of $C_{17}H_{27}NO_2$ HCl. Its molecular weight is 313.87. The structural formula is shown below.



venlafaxine hydrochloride

Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/mL in water (adjusted to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient is 0.43.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5 mg, 75 mg, or 150 mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.

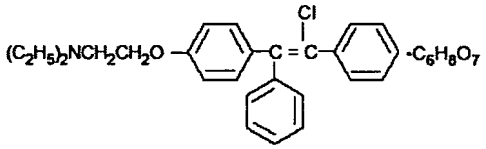
A

Clomid

Clomiphene Citrate Tablets USP

DESCRIPTION

Clomiphene citrate tablets USP is an orally administered, non steroidal, ovulatory stimulant designated chemically as 2[p-(2- chloro-1,2-diphenylvinyl) phenoxy]] trieth lamine citrate (1:1). It has the molecular formula of $C_{26}H_{28}ClNO \cdot C_6H_8O_7$ and a molecular weight of 598.09. It is represented structually as:



Clomiphene citrate is a white to pale yellow, essentially odorless, crystalline powder. It is freely soluble in methanol, soluble in ethanol; slightly soluble in acetone, water, and chloroform; and insoluble in ether. Clomiphene citrate tablets USP is a mixture of two geometric isomers [cis (zuclomiphene) and trans (enclomiphene)] containing between 30% and 50% of the cis-isomer.

Each white scored tablet contains 50 mg clomiphene citrate USP. The tablet also contains the following Inactive Ingredients: corn starch, lactose, magnesium stearate, pregelatinized corn starch, and sucrose.

C

Citalopram ODT

CITALOPRAM ODT (Citalopram HBr) Orally Disintegrating Tablets

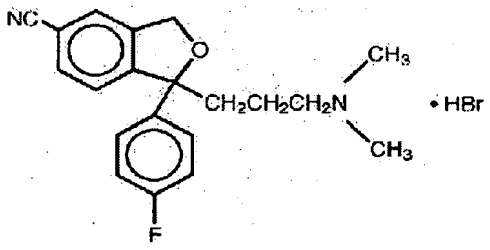
Rx Only

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. CITALOPRAM ODT is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

CITALOPRAM ODT (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated 1-[3-(dimethylamino)-propyl]-)-1-(p-fluorophenyl)- 5-phthalancarbonitrile mono-hydrobromide with the following structural formula:



The molecular formula is $C_{20}H_{21}FN_2O$ Â·HBr and its molecular weight is 405.30.

Citalopram HBr occurs as a fine white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

CITALOPRAM ODT is available as orally disintegrating tablets based on CEFORM® technology. CITALOPRAM ODT 10 mg, 20 mg and 40 mg tablets are dimpled round tablets debossed on one side containing citalopram HBr in strengths equivalent to 10 mg, 20 mg and 40 mg citalopram base.

The tablets also contain the following inactive ingredients: glyceryl distearate, stearoyl macrogolglyceride, polyacrylate dispersion 30%, hypromellose 2910, talc, mannitol, microcrystalline cellulose, low substituted hydroxypropyl cellulose, crospovidone, sodium stearyl fumarate, silicon dioxide, acesulfame potassium, monoammonium glycyrrhizinate and citric acid. In addition to the above ingredients the 10 mg tablets

D

Zoloft

ZOLOFT®

(sertraline hydrochloride)

Tablets and Oral Concentrate

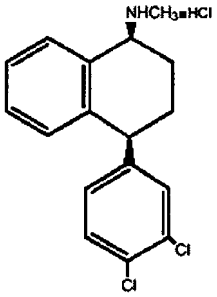
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See WARNINGS and PRECAUTIONS: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride. The empirical formula $C_{17}H_{17}NCl_2 \cdot HCl$ is represented by the following structural formula:



Sertraline hydrochloride is a white crystalline powder that is slightly soluble in water and isopropyl alcohol, and sparingly soluble in ethanol.

ZOLOFT is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25 mg tablet), FD & C Blue #1 aluminum lake (in 25 mg tablet), FD & C Red #40

B

87 48

Luvox

Fluvoxamine Maleate Tablets

Rx only

Suicidality in Children and Adolescents

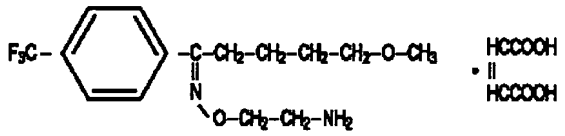
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluvoxamine or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluvoxamine is not approved for use in pediatric patients except for patients with Obsessive Compulsive Disorder (OCD). (See WARNINGS and PRECAUTIONS: Pediatric Use).

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), Obsessive Compulsive Disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the molecular formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



$C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$ **M.W. 434.4**

Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

Fluvoxamine Maleate Tablets are available in 25 mg, 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, corn starch, hypromellose (3cP), hypromellose (6cP), magnesium stearate, mannitol, methylcellulose, polyethylene glycol, polysorbate 80, pregelatinized starch,

E

Asimia

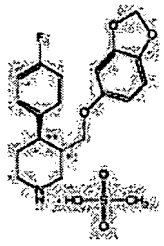
ASIMIA™

Brand of

PAROXETINE (as mesylate) tablets

DESCRIPTION

ASIMIA™ (paroxetine mesylate) is an orally administered psychotropic drug with a chemical structure related to paroxetine hydrochloride (Paxil®). It is the mesylate salt of a phenylpiperidine compound identified chemically as (-)-trans -4R- (4' - fluorophenyl) - 3S - [(3', 4-methylenedioxyphenoxy) methyl] piperidine mesylate and has the empirical formula of $C_{19}H_{20}FNO_3$ CH_3SO_3H. The molecular weight is 425.5 (329.4 as free base). The structural formula is:



Paroxetine mesylate is an odorless, off-white powder, having a melting point range of 147° to 150°C and a solubility of more than 1 g/mL in water.

Tablets

Each oval, film coated tablet contains paroxetine mesylate equivalent to paroxetine as follows: 10 mg (white); 20 mg (scored, dark orange); 30 mg (yellow); 40 mg (rose). Inactive ingredients consist of dibasic calcium phosphate, hydroxypropyl methylcellulose, hydroxypropylcellulose, magnesium stearate, sodium starch glycolate, titanium dioxide, ferric oxide red (C.I. 77491) (20-mg, and 40-mg only) and ferric oxide yellow (C.I. 77492) (20-mg, 30-mg and 40-mg only).

F

Sarafem

SARAFEM®

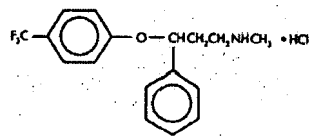
fluoxetine hydrochloride tablets

Suicidality in Children and Adolescents Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SARAFEM or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SARAFEM is not approved for use in pediatric patients. (See WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

SARAFEM® (fluoxetine hydrochloride tablets) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each SARAFEM tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol), 15 mg (48.5 µmol) or 20 mg (64.7 µmol) of fluoxetine. Each tablet also contains microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, FD&C Yellow No. 6 aluminum lake (10 mg and 20 mg tablets) and D&C Yellow No. 10 aluminum lake (10 mg and 20 mg tablets).

G